reaction has been shown to be applicable to a bile acid as a method of degradation by the conversion of cholic acid into 3,7,12-trioxy-23-aminonorcholane.

The product is different from that obtained by E. Müller in Curtius' laboratory by hydrolysis of the appropriate urethan.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC., NUTLEY, NEW JERSEY]

2-Alkylthio-5-alkyl- and 2-Alkylthio-5,5-dialkylbarbituric Acids

BY JOHN LEE

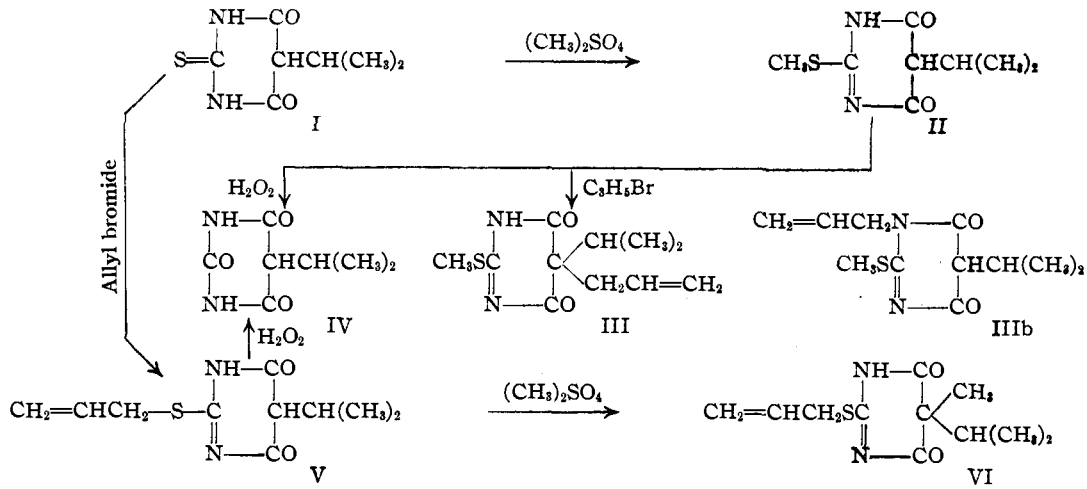
Renewed interest of late in the 5,5-dialkyl-2-thiobarbituric acids has led to the preparation of some substances of therapeutic value by the condensation of dialkyl malonic esters with thiourea.[1-3] Tabern and Volwiler[2] report that the alkylation of 5,5-dialkylthiobarbituric acids does not give crystalline products but have as yet given no report of their proposed attempt to produce these substances from alkylated thioureas. A recent patent[4] discloses such a condensation, but, as is shown later, this patent must be viewed with some reserve. The present paper reports the preparation of 2-alkylthio-5,5-dialkylbarbituric acids through the 2-alkylthio-5-alkylbarbituric acids, both types of compound being previously unknown.

In an attempt to prepare 5,5-dialkyl-2-thiobarbituric acids by the alkylation of 5-monoalkyl-2-thiobarbituric acids, it was noted that the materials so obtained were not identical with those obtained by the condensation of the corresponding 5,5-dialkylmalonic esters with thiourea. When 5-isopropyl-2-thiobarbituric acid (I) was alkylated with allyl bromide, a material melting at 224–225° was obtained, whereas 5,5-allylisopropyl-2-thiobarbituric acid, since reported in the literature,[3] has a m. p. of 176.5°. Oxidation of the new acid (V) with hydrogen peroxide gave 5-isopropylbarbituric acid (IV) identical with that produced by the condensation of urea with isopropyl diethylmalonate, showing that the allyl group was introduced into the 2-position, the product being 5-isopropyl-2-allylthiobarbituric acid (V). This reaction course seems to be general since the oxidation of the methylation product of 5-isopropyl-2-thiobarbituric acid (II) also gives 5-isopropylbarbituric acid. Alkylation with methyl sulfate therefore also introduced the methyl group on the sulfur. With ethyl sulfate under the same conditions the reaction did not proceed. With other reagents containing reactive halogen, as, for example, 2-chlorocyclohexanone, the reaction occurs and presumably takes the same course.

The 5-alkyl-2-alkylthiobarbituric acids are comparatively stable, well-crystallized materials. On long standing in air they evolve thiol-like odors. Alcoholic solutions of the acids with aqueous ferric chloride give, in the case of the methylthio compound, a violet coloration. With the higher alkylthio compounds no color reaction is obtained.

Further alkylation of the 5-alkyl-2-alkylthiobarbituric acids results in the smooth formation of trialkyl compounds. With halides the reaction is best conducted in absolute alcoholic solution, but with methyl sulfate it also proceeds in the usual manner in aqueous solution. The point of attachment of the newly introduced alkyl group is not immediately apparent. In the case of allylation of 5-isopropyl-2-methylthiobarbituric acid the structures III or IIIb might arise. Oxidation experiments on this reaction product with permanganate and with hydrogen peroxide resulted in no identifiable compounds, nor did hydrolysis with acid or alkaline solution produce any. Similar degradation experiments were attempted with the product obtained by ethylation of 5-isopropyl-2-methylthiobarbituric acid since this does not contain the easily degraded allyl group. It was expected, analogously to the production of 5-isopropyl barbituric acid from 5-isopropyl-2-methylthiobarbituric acid, that the relatively stable 5,5-ethylisopropylbarbituric acid would have been obtained if the ethyl group was attached to the 5 carbon atom. Such an acid could not be isolated. The suspicion that the newly introduced alkyl group might be attached

(1) Miller, Munch and Crossley, *Science*, **81**, 615 (1935).
(2) Tabern and Volwiler, THIS JOURNAL, **57**, 1961 (1935).
(3) Miller, Munch, Crossley and Hartung, *ibid.*, **58**, 1090 (1936).
(4) I. G. Farbenindustrie, British Patent 468,683.



to the nitrogen was voided by the determination of alkylimide and S-alkyl groups according to Vieböck and Brecker.[5] This showed that only one easily hydrolyzable alkyl group is present, and is attached to the sulfur atom. Hence it is most probable that the third alkyl group is attached to the 5 carbon atom, the compounds being 2-alkylthio-5,5-dialkylbarbituric acids.

The 5,5-dialkyl-2-alkylthiobarbituric acids are unstable substances, the crystalline materials themselves soon after crystallization evolving a strong thiol-like odor in air. On hydrolysis with 1:1 hydrochloric acid a strong disgusting odor arises, thiols apparently being split off with ease as might be expected from the constitution of the compounds. The solutions of the sodium salts formed with the molecular equivalents of sodium hydroxide decompose rapidly. The sodium salts can be shaken from their aqueous solutions with ether. Alcoholic solutions of the 5,5-dialkyl-2-alkylthiobarbituric acids on treatment with aqueous ferric chloride solution gave no color reaction.

The 5-alkyl-2-thiobarbituric acids are also not well known. Since the completion of this work 5-isopropyl-2-thiobarbituric acid[6] and 5-isobutyl-2-thiobarbituric acid[4] have been reported. Lund reports the synthesis of the former by the condensation of isopropyl diethylmalonate with thiourea in the presence of magnesium methylate in yield of 68%, whereas the corresponding ethyl diethylmalonate gives a very small yield of the 5-ethyl-2-thiobarbituric acid. It was found that by condensing isopropyl diethylmalonate with thiourea in the presence of sodium ethylate in absolute alcohol the reaction proceeds in 82% yield, and that using identical conditions with ethyl diethylmalonate a yield of only 1% was obtained. This is presumably due to the insolubility of the sodium derivative of ethyl diethylmalonate in absolute alcohol. The previously mentioned patent[4] states that allylation of 5-isobutyl-2-thiobarbituric acid with allyl bromide in benzene solution yields 5,5-allylisobutyl-2-thiobarbituric acid which is identical with that obtained by the condensation of allylisobutyl diethylmalonate with thiourea. In view of the discovery that allylation and alkylation in general with 5-isopropyl-2-thiobarbituric acid proceed with the formation of 5-isopropyl-2-alkylthiobarbituric acids and not of 5,5-allylisopropyl-2-thiobarbituric acid as would be expected by analogy to the barbituric acid series, the results reported in the patent seem deserving of further investigation. The patent also reports that 5,5-allylisobutyl-2-methylthiobarbituric acid obtained by the condensation of S-methyl-thiourea hydriodide and allyl-isobutylmalonyl dichloride can be hydrolyzed with hydrochloric acid to 5,5-allylisobutyl-2-thiobarbituric acid. In view of the complete degradation with apparent elimination of sulfur as thiol by a similar hydrolysis in the case of 5,5-allylisopropyl-2-methylthiobarbituric acid, this result seems anomalous.

Pharmacological Results.—Compounds II, V and X caused no central depression when injected intravenously in doses up to 100 mg./kg. A slight muscular tremor and acceleration of respiration was observed, the effects passing off

(5) Pregl–Roth, "Quant. organische Microanalyse," fourth edition, Verlag von Julius Springer, Berlin, 1935, p. 234.

(6) Hakon Lund, *Kgl. Danske Videnskab. Selskab. Math.-fys. Medd.*, **13**, Nr. 13, 11 pp. (1935).

TABLE I

Thiobarbituric acid	M. p., °C. uncorr.	Cryst. from	Appearance	Yield, %	Mol. formula	Analyses, %N Calcd.	Found
I, 5-Isopropyl-2-	172–173	Alcohol	Colorless sandy crystals	82	$C_7H_{10}O_2N_2S$	15.05	14.88[a]
IX, 5-Ethyl-2-	173–174	Benzene	Yellowish tinted crystals	1	$C_6H_8O_2N_2S$	16.26	16.22[b]
V, 5-Isopropyl-2-allyl-	224–225	Alcohol	Shining colorless platelets	92	$C_{10}H_{14}O_2N_2S$	12.38	12.49[b]
II, 5-Isopropyl-2-methyl-	247–248	Dioxane	Colorless crystals	80	$C_8H_{12}O_2N_2S$	13.99	14.12[b]
X, 5-Isopropyl-2-cyclohexanonyl-	>275	Dioxane	Colorless crystals	..	$C_{13}H_{17}O_3N_2S$	9.96	9.70[b]
VI, 5,5-Methylisopropyl-2-allyl-	162–163	CCl_4	Colorless platelets	32	$C_{11}H_{16}O_2N_2S$	11.66	11.57[a]
III, 5,5-Allylisopropyl-2-methyl-	122.5–123	*i*-PrOH	Colorless platelets	43	$C_{11}H_{16}O_2N_2S$	11.66	11.77[a]
VII, 5,5-Isoamylisopropyl-2-methyl-	130–130.5	AcOEt	Shining hexagonal plates	38	$C_{13}H_{22}O_2N_2S$	10.84	10.59[b]
VIII, 5,5-Ethylisopropyl-2-methyl-	133–134	Aq. acetone	Colorless crystals	28	$C_9H_{16}O_2N_2S$	12.96	13.03[b]

[a] Kjeldahl analysis. [b] Micro-Dumas analysis.

rapidly. This result with the 5-monoalkylated-2-thiobarbituric acids was not unexpected since it is well known that 5-monoalkylated barbituric acids have no central depressant effect. The results with compound VI were identical. Here, one of the alkyl groups attached to the 5-position is a methyl group, and it has been observed in the barbituric acid series that for a central depressant effect it is necessary that each of the attached radicals contain at least two carbon atoms.

The 2-alkylthio-5,5-dialkylbarbituric acids III, VII and VIII possessed depressant effects, and in addition certain strychnine-like effects. Compound III showed the greatest depressant and the lowest convulsant effects, both of which were of short duration. Narcosis was not produced by any of the compounds in doses up to 100 mg./kg. administered intravenously to rabbits.

The pharmacological work was performed in the Nutley Pharmacology Laboratory of Hoffmann–La Roche, Inc., by Dr. R. H. K. Foster to whom I am indebted for the above results.

Experimental

The following experiments were selected as being illustrative of the methods employed. The data on the compounds are given in Table I.

5-Alkylthiobarbituric Acid

5-Isopropyl-2-thiobarbituric Acid.—Two hundred and two grams of isopropyl diethylmalonate and 83 g. of thiourea (10% excess) were dissolved in 400 cc. of absolute alcohol under reflux. A solution of sodium ethylate formed by adding 46 g. of sodium to 600 cc. of absolute alcohol was added to the solution under reflux. The mixture was refluxed for seven hours, stood overnight, the alcohol distilled off under vacuum, the residue taken up in water, ice added, and made acid to congo paper with 10% sulfuric acid. The precipitate was filtered off, washed with water, and crystallized from absolute alcohol.

5-Alkyl-2-alkylthiobarbituric Acids

5-Isopropyl-2-methylthiobarbituric Acid.—Twenty-three and one-quarter grams of 5-isopropyl-2-thiobarbituric acid was dissolved in 375 cc. of normal sodium hydroxide, 15.8 g. of methyl sulfate added at once and the mixture stirred until the methyl sulfate had disappeared. The solution after cooling with ice was made acid to congo paper with 10% hydrochloric acid, the precipitate filtered off, crystallized from isopropyl alcohol and then from dioxane; yield 19.8 g.

Oxidation of 5-Isopropyl-2-methylthiobarbituric Acid.—Ten grams of the above acid was dissolved in 120 cc. of hot acetic acid; 19 g. of lead acetate in 60 cc. of hot water was added, the mixture cooled to 40° and 18.5 g. of 30% hydrogen peroxide was dropped in during three-fourths of an hour. The temperature was then raised to 60° for three-fourths of an hour and the mixture stood at room temperature overnight. Some precipitated lead sulfate was filtered off, 100 cc. of hot water added, and the lead removed with hydrogen sulfide. After filtration the aqueous acetic acid solution on concentration in vacuum separated crystals of unchanged 5-isopropyl-2-methylthiobarbituric acid. Evaporation of the mother liquors left a crystalline mush which was taken up in acetone and filtered. The acetone extract on evaporation to dryness gave a sticky mass which was recrystallized from isopropyl alcohol; m. p. 210–211°, uncorr. A mixed m. p. with 5-isopropylbarbituric acid 210–211° uncorr., showed no depression.

Anal. Calcd. for $C_7H_{10}O_3N_2$: N, 16.48. Found: N, 16.62, 16.73.

5-Isopropyl-2-cyclohexanonylthiobarbituric Acid.—4.65 grams of 5-isopropyl-2-thiobarbituric acid was dissolved in 25 cc. of normal sodium hydroxide solution, a trace of copper powder added, and 5 g. of 2-chlorocyclohexanone (50% excess) in enough alcohol to form a homogeneous mixture. After standing at room temperature for three days the alcohol was driven off on the water-bath, water added, the insoluble material filtered off, taken up in 25 cc. of normal sodium hydroxide, filtered, and made acid to congo paper with dilute hydrochloric acid. The white precipitate formed was filtered off, washed with water and dried in a vacuum at 25°. It is insoluble in ethyl alcohol, methyl alcohol, acetone, benzene, chloroform, and ethyl acetate. Crystallized from dioxane it does not melt under 275°.

5,5-Dialkyl-2-alkylthiobarbituric Acids

5,5-Allylisopropyl-2-methylthiobarbituric Acid.—Twenty grams of 5-isopropyl-2-methylthiobarbituric acid was mixed with 25 cc. of absolute alcohol and 41 cc. of 2.435 normal sodium ethylate solution added. A solution formed to which 12 cc. of allyl bromide and 20 drops of pyridine (catalyst) were added. After refluxing for forty-five minutes the sodium bromide was filtered off, the

excess allyl bromide and solvent removed from the filtrate by distillation in vacuum, the residue taken up in ether, and 4 volumes of petroleum ether added. This left a crystalline residue of 7 g. of unchanged 5-isopropyl-2-methylthiobarbituric acid. The petroleum ether solution on concentrating to one-third of its volume and standing in the ice-box gave a white crystalline precipitate which on crystallization from dioxane and recrystallization from isopropyl alcohol amounted to 10.5 g.; yield 43%.

5,5-Ethylisopropyl-2-methylthiobarbituric Acid.—This was prepared in the same manner as the above.

Anal.[7] Combined alkylimide and S-alkyl determination[5]: 3.956 mg. of substance distilled to 140°; 5.75 cc. of 0.02 *N* $Na_2S_2O_3$. Found: $S(CH_3)$, 7.28; calcd. $S(CH_3)$, 6.94. 5.112 mg. of substance twice distilled to 360°: 7.83 cc. of 0.02 *N* $Na_2S_2O_3$. Found: $S(CH_3)$, 7.67.

(7) Performed by Mr. J. F. Alicino, Chemistry Department, Fordham University.

Summary

1. 5-Alkyl-2-alkylthiobarbituric acids have been prepared by the alkylation of 5-alkyl-2-thiobarbituric acid.

2. 5,5-Dialkyl-2-alkylthiobarbituric acids have been prepared by the alkylation of 5-alkyl-2-alkylthiobarbituric acids.

3. The 5-alkyl-2-alkylthio- and the 5,5-dialkyl-2-alkylthiobarbituric acids prepared are shown to have no promise of value as hypnotics.

NUTLEY, NEW JERSEY RECEIVED JANUARY 17, 1938

[CONTRIBUTION FROM GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 640]

The Molecular Structures of the Methyl Derivatives of Phosphorus and Arsenic

BY H. D. SPRINGALL[1] AND L. O. BROCKWAY

The electron diffraction investigation of the fluorides and chlorides of silicon, germanium, tin, phosphorus and arsenic,[2] and some fluorine derivatives of carbon, shows bond distances shorter than those calculated by the addition of the corresponding covalent radii.[3] It was suggested that two effects might be responsible for this shortening: (a) an extra ionic character of the bonds which is not present in the compounds from which the table of radii was constructed; and (b) the contribution of some double bond character due to resonance of the molecule among several structures some of which have one or more double bonds. Since structures with double bonds are not possible in the methyl compounds of the elements concerned, a study of these methyl compounds was proposed as a means of distinguishing between the two effects and of testing the covalent radii. Brockway and Jenkins[4] investigated the tetramethyl compounds of silicon, germanium, tin and lead, trimethyl nitrogen, and the dimethyl compounds of sulfur and mercury. This work has now been extended by the investigation of trimethylphosphine and trimethylarsine.

(1) Commonwealth Fund Fellow.

(2) L. O. Brockway and F. T. Wall, THIS JOURNAL, **56**, 2373 (1934); L. O. Brockway, *ibid.*, **57**, 958 (1935).

(3) (a) L. Pauling, *Proc. Nat. Acad. Sci.*, **18**, 293 (1932); (b) N. V. Sidgwick and E. J. Bowen, *Ann. Rep. Chem. Soc.*, **28**, 384 (1931); (c) L. Pauling and M. L. Huggins, *Z. Krist.*, **87**, 205 (1934).

(4) L. O. Brockway and H. O. Jenkins, THIS JOURNAL, **58**, 2036 (1936).

The apparatus for obtaining the photographs and the method of interpreting the results are those described by Brockway.[5] Both compounds were photographed with electrons having wave length 0.0613 Å. and with a camera distance of 10.87 cm.

Trimethylphosphine.—This substance was prepared in collaboration with Dr. D. Purdie in Stanford University, by the Grignard reaction (CH_3MgI on PCl_3) based on the method of Hibbert,[6] using the stable $[AgIP(CH_3)_3]_4$ complex,[7] for separation and transportation. On heating *in vacuo*, the complex dissociated, and the trimethylphosphine distilling off was condensed at liquid air temperature.

Theoretical intensity curves were calculated for pyramidal models having the phosphorus atom at the apex, and with C–P–C angles of 104, 100 and 96°.

For the 100° model two curves were calculated. One, A, included all interatomic distance terms except the H–H ones. In this the values for the non-bonded C–H distances were calculated by ignoring the free rotation of the methyl groups and treating one "fixed" model in which one of the H atoms of each methyl group is located in that one of the three planes of symmetry of the

(5) L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

(6) H. Hibbert, *Ber.*, **39**, 161 (1906).

(7) F. G. Mann, A. F. Wells and D. Purdie, *J. Chem. Soc.*, 1828 (1937), and unpublished communications.